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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,101	02/19/2002	Klaus Gregorius Nielsen	674542-2003	7906

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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,101	NIELSEN ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *26-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims **1-25**) in the Response filed 15 December 2003 is acknowledged. The traversal is on the ground(s): **(a)** Groups I and II both are related, **(b)** the claims of Group II depend from the claims of Group I, **(c)** Groups I and II may be searched without serious burden, **(d)** the method of Group II use the composition of Group I, and **(e)** both Groups I and II were proposed to be classified in class 536, subclass 23.1. This is not found persuasive because the claims of Group I are drawn to a product and Group II are drawn to a method of use. Regardless of relation and dependency, the methods as delineated by Group II are not the only possible method of use. Group I requires search and consideration of the immunogen itself while Group II requires search and consideration of immunization protocols, thus the searches are not co-extensive. Group I should be classified in class 424, subclass 188.1 while Group II should be classified in class 514, subclass 1. Therefore, Group I and Group II are distinct and independent.

2. Applicant's election of "a bond cleavable by a peptidase" is acknowledged. This second restriction requirement as set forth in the previous Office Action (13 November 2003) is hereby *withdrawn.*

3. Claims **1-25** are under examination. Claims **26-38** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims **1-25** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an immunogen comprises an Aβfragment (SEQ ID NO: 2, residues 673-714), P2, and P30 coupled to a pharmaceutically acceptable activated polyhydroxypolymer carrier*, does not reasonably provide enablement for *other antigenic determinants or epitopes*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

5. The claims as currently presented are drawn very broadly to an immunogen comprises at least two antigenic determinants wherein in one is at least one B-cell epitope and/or least one CTL epitope and the other includes a T helper cell epitope coupled to a pharmaceutically acceptable activated polyhydroxypolymer carrier. The language of said claims encompasses enormous and undefined genuses of antigenic determinants. The open claim language widens the scope of the claims to include any compositions with any embodiment having these three components: a B-cell epitope or CTL epitope, a T helper cell epitope, and a polyhydroxypolymer.

6. The specification teaches that immunogenic peptides can be coupled to a polyhydroxypolymer carrier along with B-cell, CTL, and/or T helper cell epitopes.

7. However, the specification fails to provide any guidance for the successful construction of any immunogen save one comprising an immunogen comprises an Aβ fragment (SEQ ID NO: 2, residues 673-714), P2, and P30 coupled to a pharmaceutically acceptable activated polyhydroxypolymer carrier. Due to the ponderous breadth of epitopes included in the claims, the resolution of the various complications in regards to possible immungens is highly unpredictable. Thus one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known epitopes to correlate with the desired properties. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an immunogen *in vivo* based solely on the construction and use of a single example as highly problematic (see MPEP §2164.02). The sheer number of possible combinations presents an onerous burden on the skilled artisan to successfully use the embodiments of the claims. As noted in the art below, immunogens are unpredictable and vary greatly according to species, condition, humoral versus cellular immunity, and their general efficacy. Thus, although the specification prophetically considers and discloses general methodologies of using a single member of the genus of immunogens claimed, such a disclosure would not be considered

enabling since the state of immunology is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of immunology.

10. The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition (in an epitope), see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological

function and immunological recognition are unpredictable properties which must be experimentally determined.

11. Furthermore, on the breadth of the claims, Otvos, Jr. *et al.* (13 January 2000) "In situ stimulation of a T helper cell hybridoma with a cellulose-bound peptide antigen." Journal of Immunological Methods **233**(1-2): 95-105 teaches that only one T cell epitope out of 40 known stimulated a hybridoma when conjugated to cellulose (Figure 1). Thus even though the epitopes were all known T cell epitopes experimentation and a high rate of failure was entailed in confirming which one would work when conjugated to cellulose. A similar pattern is presented with the instant claims. Only the broad genuses of B-cell, CTL, and TH epitopes are listed in claim 1 but no specific epitopes or conserved structure to provide guidance as to what is sufficient and necessary to practice the invention.

12. On the nature of the invention, Calvo-Calle *et al.* (15 February 1993) "Immunogenicity of Multiple Antigen Peptides Containing B and Non-Repeat T cell Epitopes of the Circumsporozoite Protein of *Plasmodium falciparum*." The Journal of Immunology **150**(4): 1403-1412 teaches an analogous construct to the instant invention where B-cell and T-cell epitopes are conjugated to carrier molecule (Figure 1). Calvo-Calle *et al.* demonstrates that the antibody titers produced by similar epitopes on their construct vary greatly, even though the epitopes are closely related (Table 1). Therefore taking the enormous breadth of the claims, it would entail undue experimentation to practice the claims to the full extent due to the unpredictability of the resultant immune response to any given epitope.

13. On the state of the prior art, Marguerite *et al.* (June 1992) "Analysis of antigenicity and immunogenicity of five different chemically defined constructs of a peptide." Molecular

Immunology **29**(6): 793-800 teaches that while conjugating B- and T-cell epitopes to a carrier to boost responses is desirable it poses the problems of scale-up, stability, and control of the immune response (pp. 793). In addition, Marguerite *et al.* also shows the variety of results of using different epitopes, both conjugated and non-conjugated, in stimulating immune responses (Figures 3 and 4). Thus the skilled artisan is confronted with a burden of undue experimentation to determine which epitopes, how many, and conjugated to which carrier will satisfy the claims.

14. On the level of predictability in the art, Sela *et al.* (April 1992) "A Tale of Two Peptides, TyrTyrGluGlu and TyrGluTyrGlu, and their Diverse Immune Behavior." Behring Inst. Mitt. **91**: 54-66 teaches that tow major B and T cell epitopes, TyrTyrGluGlu and TyrGluTyrGlu although essentially identical in their molecule weight, size, shape, and composition have profound differences in their immunogenecity (pp. 54). For instance, TyrTyrGluGlu is a major B cell epitope and TyrGluTyrGlu is a major T cell epitope. TyrTyrGluGlu is thymus dependent while TyrGluTyrGlu is thymus independent. The difference between these largely identical epitopes is believed to be their three dimensional structure (pp. 64-65). Therefore a small change in amino acid sequence or three-dimensional structure can radically alter the immunogenicity of an epitope. Thus the skilled artisan is practicing the instant invention largely without guidance in an unpredictable field of endeavor.

15. Further Goldsby *et al.* (2002) Kuby Immunology Chapter 1 "Overview of the Immune System" (pp. 3-25) and Chapter 18 "Vaccines" (pp. 449-465) teach that the development of an immune response does not necessarily mean that a state of protective immunity has been achieved. Secondly, the development of immunological memory is crucial for successful use of an immunogen (or vaccine) (pp. 454). Also the claims as currently presented to not specify a

target antigen, disease, condition, disorder, infection, or malady to which the immunogen is to be used. As Goldbsy *et al.* (2002) teach the consequences of immune dysfunction it is necessary to specify which antigen will comprises the immunogen so the skilled artisan is apprised of the use thereof (pp. 21-23).

16. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from a single example to the full scope of the claims as exemplified in the references herein.

17. Claims **1-25** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. Independent claim 1 require antigenic determinant that includes at least one B-cell and/or at least on CTL epitope and at least one second antigenic determinant that includes a T helper cell epitope while practicing the claimed methods thus implying that the activity of the agent used is not known or must be confirmed. The claims do not require that the epitope possess any particular conserved structure, or other distinguishing feature. Thus, the claims are drawn to a genus of antigenic determinants that is defined by desired activity.

19. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making

the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is the recitation of desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

20. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

21. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain

without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

22. Further more the claims encompass producing antibodies versus an undefined antigen. The claims fail to specific an epitope or require that the antibody's target possess any particular conserved structure, or other distinguishing feature, such as a sequence. Thus, the claims are drawn to a genus of antibodies that is defined by binding anywhere, anyhow to a generic immunogen.

23. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently

disclosed is a recitation of a desired target specificity for the antibody in question. The specification does not identify any particular portion of the target (i.e. Aβ residues) that must be conserved, nor does it provide an epitope. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

24. In *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 20 January 2004) the CAFC held that "Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

25. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR

antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application.

26. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen."

27. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

28. Claim **25** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation "a particle" has not known metes and bounds. Nor is it sufficiently defined by the specification or the prior art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims **1, 16, 18, 19,** and **21** rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/20027 (13 April 2000) Steinaa *et al.*

30. The claims as currently presented are drawn very broadly to an immunogen comprises at least two antigenic determinants wherein in one is at least one B-cell epitope and/or least one CTL epitope and the other includes a T helper cell epitope coupled to a pharmaceutically acceptable activated polyhydroxypolymer carrier. The open claim language widens the scope of the claims to include any compositions with any embodiment having these three components: a B-cell epitope or CTL epitope, a T helper cell epitope, and a polyhydroxypolymer.

31. WO 00/20027 teaches an immunogen comprising: 1) at least on CTL epitope derived and/or at least one B-cell epitope and 2) at least one T helper cell epitope (T_H epitope) coupled to a dextran molecule which is a pharmaceutically acceptable carrier thus meeting the limitations of claim 1 (pp. 12, 30, and 96).

32. WO 00/20027 teaches the immunogen wherein at least one moiety stimulates the immune system thus meeting the limitations of claim 16 (pp. 31).

33. WO 00/20027 teaches the immunogen wherein at least one CTL epitope when presented is associated with an MHC Class I molecule on the surface of the APC and/or wherein said at least one first foreign TH epitope when presented is associated with an MHC class II molecule on the surface of the APC thus meeting the limitations of claims 18 and 19 (pp. 156).

34. WO 00/20027 teaches the immunogen wherein it is in conjunction with an adjuvant selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine, and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (ISCOM matrix); a particle; DDA; aluminum adjuvants; DNA adjuvants; γ-inulin; and an encapsulating adjuvant thus meeting the limitations of claim 25 (pp. 161).

35. Claims **1, 2, 6, 11, 12, 14, 17, 20,** and **21** rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/23076 (25 November 1993) Cheronis.

36. The claims as currently presented are drawn very broadly to an immunogen comprises at least two antigenic determinants wherein in one is at least one B-cell epitope and/or least one CTL epitope and the other includes a T helper cell epitope coupled to a pharmaceutically acceptable activated polyhydroxypolymer carrier. The open claim language widens the scope of the claims to include any compositions with any embodiment having these three components: a B-cell epitope or CTL epitope, a T helper cell epitope, and a polyhydroxypolymer.

37. WO 93/23076 teaches an immunogen comprises fluorescein (Fl) and chicken ovalbumin (residues 323-339) coupled to dextran (Example 2). This immunogen is injected into mice therefore is a "pharmaceutically acceptable" thus meeting the limitations of claim 1. F1 stimulates B-cells, the ovalbumin peptide stimulates T helper cells, and dextran is a polyhydroxypolymer carrier of 500,000 MW thus meeting the limitations of claims 1, 2, 11, 12, 14, and 20 (pp. 13-15). In addition, F1 and the ovalbumin peptide do not derived from the same species and the latter is a peptide thus meeting the limitations of claims 17 and 22 (pp. 13-15). Dextran is a polyhydroxypolymer carrier which does not contain any amino acids thus meeting the limitations of claim 6 (pp. 13).

Summary

38. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
March 10, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER